04-28-06

AF PGJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	SHI et al.	Group Art Unit:	1617
Serial No.:	09/438,206	Examiner:	HUI, San Ming R
Filed:	12 November 1999	Docket No.:	290.00420101
		Confirmation No.:	9018

Title: METHODS AND COMPOSITIONS FOR TREATING MAMMALIAN SPINAL CORD INJURIES

Commissioner for Patents
Mail Stop Appeal Brief – Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

X An itemized return postcard.
__ A Petition for Extension of Time for _ month(s).
__ An Information Disclosure Statement (__ pgs); copies of ___ applications; 1449 forms (__ pgs); and copies of ___ documents cited on the 1449 forms.
__ A request for continued examination (RCE) and a check in the amount of $_, for the required filing fee.
X A Reply Brief (13 pages total);
X Please charge any necessary fees to Deposit Account No. 13-4895.
__ Other:
__ Amendment ___ No Additional fee is required. ___ The fee has been calculated as shown:

Fee Calculation for Claims Pending After Amendment

	Pending Claims after Amendment (1)	Claims Paid for Earlier (2)	Number of Additional Claims (1-2)	Cost per Additional Claim	Additional Fees Required
Total Claims				x $50 =	
Independent Claims				x $200 =	
One or More New Multiple Dependent Claims Presented? If Yes, Add $360 Here →					
Total Additional Claim Fees Required					

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895. Triplicate copies of this sheet are enclosed.

MUETING, RAASCH & GEBHARDT, P.A.
Customer Number: 26813

By: Nancy A. Johnson
Name: Nancy A. Johnson
Reg. No.: 47,266
Direct Dial: 612-305-4723
Facsimile: 612-305-1228

CERTIFICATE UNDER 37 CFR §1.10::
"Express Mail" mailing label number: EV405491877US Date of Deposit: 27 April 2006
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to: **Mail Stop Appeal Brief – Patents** Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Jacquelyn K. Torborg
Name: JACQUELYN K TORBORG

(LARGE ENTITY TRANSMITTAL UNDER RULE 1.10)

PATENT
Docket No. 290.00420101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Shi et al.	Group Art Unit:	1617
Serial No.:	09/438,206	Examiner:	Hui
Confirmation No.:	9018		
Filed:	12 November 1999		

For: METHODS AND COMPOSITIONS FOR TREATING MAMMALIAN SPINAL CORD INJURIES

REPLY BRIEF

Commissioner for Patents
Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is presented under 37 C.F.R. § 41.41 in response to the Examiner's Answer, mailed February 27, 2006, which was in turn mailed in response to the Appeal Brief filed on March November 23, 2005, for the above-identified application

This Brief is being submitted as set forth in 37 C.F.R. § 41.41. Please charge any fees, if applicable, to Deposit Account No. 13-4895 for filing this Brief under 37 C.F.R. § 41.20(b)(2).

TABLE OF CONTENTS

I. STATUS OF CLAIMS

Claims 1-21, 31-37, 41, and 42 having been canceled, the pending claims are claims 22-30, 38-40, 43, and 44. Rejected claims 22-30, 38-40, 43, and 44 are the subject of this Appeal (see Claim Appendix in the Appeal Brief filed November 23, 2005).

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the Examiner's Answer mailed February 27, 2006, the Examiner withdrew the rejection of claims 22-30, 38, 40, 43, and 44 under 35 U.S.C. §112, first paragraph, that the specification does not reasonably provide enablement for 20-40% PEG. This rejection corresponds to Section A2 in the Grounds of Rejection to Be Reviewed on Appeal (page 4 of the Appeal Brief, filed November 23, 2005).

In the Examiner's Answer mailed February 27, 2006, the Examiner stated that "the outstanding provisional obviousness double patenting [rejection of claims 22-29, 38, and 39 over claims 1-17 of copending Application No. 10/132,542] is maintained while the terminal disclaimer filed November 23, 2005, is being processed. Once the terminal disclaimer is approved, the obviousness double patenting rejection will be withdrawn" (page 9, section (9), Examiner's Answer mailed February 27, 2005). This rejection corresponds to Section B in the Grounds of Rejection to Be Reviewed on Appeal.

No new grounds of rejection were presented.

The rejections remaining applicable to the appealed claims are as follows:

A1. Claims 22-30, 38, 40, and 44 stand rejected under 35 U.S.C. §112, first paragraph, as claiming subject matter not enabled by the specification.

B. Claims 22-29, 38, and 39 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/132,542.

C. Claims 22, 24-30, 38-40, 43, and 44 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian (U.S. 5,382,584) in view of Potter et al. (Clin Invest Med, 19(4), Suppl.:S80, #533).

D. Claims 22-30, 38-40, 43, and 44 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shulman (U.S. 4,599,354) in view of Edwards (U.S. 4,369,769).

III. ARGUMENT

A1. Claims 22-30, 38, 40, and 44 are enabled by the specification; they meet the requirements of 35 U.S.C. §112, first paragraph.

Claims 22-30, 38, 40, and 44 remain rejected under 35 U.S.C. §112, first paragraph. In particular, the Examiner asserts, that "[f]rom the teachings of Shelby [*sic*] . . . it is known that PEG 4000 would cause dissolution of myelin and may cause manifestations of the loss of neural function," thus while being enabling for polyethylene glycol ("PEG") with a molecular weight of 40 to 3500 daltons, the specification does not reasonably provide enablement for PEG 4000 (page 4, Examiner's Answer mailed February 27, 2006). Appellants' arguments set forth in the Appeal Brief mailed November 23, 2005, in response to this rejection are maintained and supplemented herewith.

Appellants submit that the Examiner is ignoring the innovative showings of the present invention. With the present invention, "[i]t has been discovered that contacting an injured spinal cord of a vertebrate with a biomembrane fusion agent treats cellular damage such that function is at least partially restored. . . . In one form of the invention, the biomembrane fusion agent is a polyalkylene glycol, such as polyethylene glycol" (page 3, lines 2-9 of the specification). The specification teaches that "no specific PEG molecular weight is critical to the process" (page 27, lines 7-8 of the specification). With the methods of the present invention, the application of the biomembrane fusion agent to injured nervous tissue results in the molecular repair and fusion of nerve membranes and the reconnection and repair of injured nervous system tissue (page 36, lines 10-13 and page 46, lines 25-27 of the specification). Although not being limited to a single theory, Appellants submit that it is this "sealing" behavior of the biomembrane fusion agent which restores excitability and reverses anatomical dissolution of the nerve fiber after injury (see page 28, lines 11-13 of the specification). Appellants further submit that by noting the "dissolution" of myelin with the application of PEG 4000," Selby is confirming the ability of PEG to function as a "biomembrane fusion agent" in the methods of the present invention, fusing

and sealing biomembranes.

Appellants submit that the teachings of Selby must be interpreted in their limited context; a short correspondence, cautioning medical practitioners to "avoid the use of Depro-Medrol in and about any nervous elements." Appellants submit that Selby provides no evidence establishing that PEG 4000 will not work in the methods of the present invention, comprising contacting an injured spinal cord with an effective amount of at least one C1-C10 polyalkylene glycol or polyethylene glycol, wherein the effective amount of the at least one C1-C10 polyalkylene glycol or the polyethylene glycol is effective to restore nerve impulse conduction through said injured spinal cord.

Finally, Appellants are confused by the Examiner's position, expressed later in the Examiner's Answer, that, rather than teaching the application of a formulation of PEG 4000 to tissues of the nervous system, Selby teaches the application of a PEG 3350 formulation (second complete paragraph, page 12 of Examiner's Answer mailed February 27, 2006). Indeed, the product information given for Depo-Medrol on pages 2600-2602 of the Physicians Desk Reference ("PDR") for 1996 (entered into the record by citation within the Final Office Action mailed November 23, 2001) does teach that Depo-Medrol contains polyethylene glycol 3350. Appellants acknowledge the Examiner's statement that the specification is enabling for PEG with a molecular weight of 40 to 3500 daltons (first paragraph, page 4, Examiner's Answer mailed February 27, 2006). Thus, Appellants submit that the Examiner's assertion that "in view of the teachings of Shelby [*sic*], the employment of PEG 4000 is not enabled by the instant specification" (page 4, Examiner's Answer) cannot be sustained in view of the Examiner's acknowledgement that Selby utilizes a PEG 3350 formulation and not a PEG 4000 formulation.

Appellants submit that the teachings of Selby do not support the Examiner's assertion that the specification does not reasonably provide enablement for PEG 4000. For at least the reasons set forth herein and previously of record, it is respectfully submitted that the specification enables any person skilled in the art to which it pertains, or is most nearly connected, to make and use the invention commensurate with the scope of claims 22-30, 38, 40, and 44. Review and reversal of

this rejection by the Board is respectfully requested.

B. Withdrawal of the provisional rejection of claims 22-29, 38, and 39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/132,542 is requested in view of Terminal Disclaimer submitted herewith.

Claims 22-29, 38, and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/132,542 (page 3-4, Office Action mailed February 23, 2005). Appellants respectfully submit that the Terminal Disclaimer submitted along with the Appeal Brief filed November 23, 2005, is in compliance with 37 CFR 1.321(c) and thereby obviates the Examiner's double patenting rejection of pending claims 22-29, 38, and 39. Appellants respectfully request that this rejection be withdrawn.

C. Claims 22, 24-30, 38-40, 43, and 44 are patentable under 35 U.S.C. §103(a) over Balasubramanian (U.S. 5,382,584) in view of Potter et al. (Clin Invest Med, 19(4), Suppl.:S80, #533).

Claims 22, 24-30, 38-40, and 43-44 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian (U.S. Patent No. 5,382,584) in view of Potter et al. (Clin. Invest Med, 1996;19(4) Suppl. S80 #533). Appellants' arguments set forth in the Appeal Brief mailed November 23, 2005, in response to this rejection are maintained and supplemented herewith.

Appellants respectfully submit that Balasubramanian in view of Potter does not teach contacting an injured spinal cord with *an effective amount* of at least one C1-C10 polyalkylene glycol or polyethylene glycol, wherein *the effective amount* of the at least one C1-C10 polyalkylene glycol or the polyethylene glycol *is effective to restore nerve impulse conduction through said injured spinal cord.* In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that Balasubramanian "teaches the effective amount that would

result in the recited effect when applied to the injured spinal cord" (page 11, Examiner's Answer mailed February 27, 2006). Appellants disagree and submit that Balasubramanian teaches polyethylene glycols only for use as non-toxic, inert, and pharmaceutically acceptable carriers (column 5, line 11 to column 6, line 27) in the preparation of pharmaceutical compositions of adenosine reuptake inhibitors.

In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that "a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present" (bridging pages 11-12 of Examiner's Answer mailed February 27, 2006). Appellants respectfully submit that the Examiner is failing to appreciate that the instant claims are not drawn to a chemical composition. Rather, the claims of the present invention are drawn to methods of treating a mammalian patient having suffered an injury to its spinal cord. Appellants submit that the claimed methods, comprising contacting an injured spinal cord with *an effective amount* of at least one C1-C10 polyalkylene glycol or polyethylene glycol, wherein *the effective amount* of the at least one C1-C10 polyalkylene glycol or the polyethylene glycol *is effective to restore nerve impulse conduction through said injured spinal cord* are not, as asserted by the Examiner, "necessarily present" in the teachings of Balasubramanian.

The Examiner asserted that "[t]he motivation to combine the teachings of Balasubramanian and Potter is based on the fact that 4-aminopyridine is known to be useful as a treatment for spinal cord injury. . . . Absent evidence to the contrary, employing [PEG and 4-aminopyridine] concomitantly for treating the very same condition, spinal cord injuries, would be obvious (*In re Kerkhoven* 205 USPQ 1069)" (page 12, Examiner's Answer mailed February 27, 2006). As previously presented (page 14, Appeal Brief filed November 23, 2005), Appellants strongly disagree and respectfully submit that the Examiner is misapplying the holding of *In re Kerkhoven*. With *In re Kerkhoven*, the court held that "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, *in order to form a third composition which is to be used for the very same purpose*. . . . [T]he idea

of combining them flows logically from their having been individually taught in the prior art" (*In re Kerkhoven* 626 F.2d 846, 850 205 USPQ 1069, 1072 (CCPA 1980 (emphasis added)). Appellants submit that the holding of *In re Kerkhoven* pertains to compositions and is not relevant to the claimed methods of treatment. Further, Appellants submit that Balasubramanian in view of Potter does not each teach compositions which are useful for the same purpose. Rather, Balasubramanian makes a passing reference to compositions including polyethylene glycol as an inert carrier. Potter teaches compositions of 4-aminopyridine for the treatment of nerve demyelination. These are distinctly different purposes. One of ordinary skill in the art would not be motivated to combine the teachings of Balasubramanian with the teachings of Potter to obtain the method of claims 22-30, 38-40, 43, and 44, directed to treating a mammalian patient having suffered an injury to its spinal cord, comprising contacting the injured spinal cord with a composition comprising an effective amount of at least one C1-C10 polyalkylene glycol (claims 22-30 and 44) or polyethylene glycol (claims 38, 40, 43, and 44), wherein the effective amount of at least one C1-C10 polyalkylene glycol or polyethylene glycol is effective to restore nerve impulse conduction through the injured spinal cord.

In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that "Appellant's arguments . . . averring the teaching away from Selby are not convincing. The formulation Selby provided contains PEG 4000. However, the formulation cited by the PDR reference is not PEG 4000. It is rather PEG 3350. Therefore, the arguments are not convincing" (page 12, Examiner's Answer mailed February 27, 2006). Appellants do not understand the Examiner's assertions. The Examiner relies on the teachings of Selby, of the application of a PEG 4000 formulation, to substantiate the rejection of the claims 22-30, 38, 40, and 44 under 35 U.S.C. §112, first paragraph, asserting that "[f]rom the teachings of Shelby [*sic*] . . . it is known that PEG 4000 would cause dissolution of myelin and may cause manifestations of the loss of neural function" (page 4, Examiner's Answer mailed February 27, 2006). Now, on page 12 of the same Examiner's Answer, the Examiner takes a contradictory position, asserting that Selby teaches that PEG 3350, and not PEG 4000, is associated with myelin dissolution. Clarification is

requested concerning the Examiner's contradictory positions. Appellants continue to submit that the teachings of Selby and of Benzon et al. both express concerns over the harmful effects of administering polyethylene glycol to nervous tissue, thereby teaching *away* from combining the teachings of Balasubramanian and Potter, and *away* from the claimed invention.

In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that "Appellants arguments . . . averring the presence of unexpected results are not convincing" (page 12, Examiner's Answer mailed February 27, 2006). Specifically, the Examiner asserted that "[t]he disclosure[s] in page 13, line 26 to page 14, line 2 are merely statements [not] supported by any evidence or data." Citing MPEP 716.02 and MPEP 716.02(a)-(g), the Examiner stated "that it is the appellant's burden to demonstrate unexpected results over the prior art" and asserted that the specification includes "no data to evaluate unexpected results. Therefore, unexpected results are not seen to be present" (page 12-13, Examiner's Answer mailed February 27, 2006).

Appellants adamantly, yet respectfully, disagree. First, Appellants do not understand the Examiner's reliance on chapter 716 of the MPEP, "Affidavits or Declarations Traversing Rejections, 37 CFR 1.132." Appellants have not submitted declaratory evidence pertaining to unexpected results. Rather, Appellants are relying on the teachings and examples provided by the specification itself. Appellants submit that the specification provides adequate data substantiating the synergistic results obtained by treatment with both a fusion agent and a potassium channel blocker. For example, Appellants direct the Examiner and the Board to the following portions of the specification:

> Moreover, it has unexpectedly been discovered that treatment of an injured mammalian spinal cord with a potassium channel blocker, such as 4-aminopyridine, after treatment with a fusion agent, such as polyethylene glycol, can result in synergistic repair of the spinal cord. For example, CAPs increase in coordination when both agents are used by a percentage greater than the sum of the percent increase in conduction of the CAPs when injured spinal cords are treated alone with either the fusion agent or the potassium channel blocker. (page 13, line 26 to page 14, line 2 of the specification);

> [W]e tested the response of "recovering" axons to the additional application of the fast potassium channel blocker, 4-aminopyridine (4-AP). In this trial, 5 separate controls were treated with an application of PEG as described above and compared to five control cords. One hour after compression, 100 μM 4-AP (in Kreb's solution) was applied as described above. (page 20, lines 6-12 of the specification); and
>
> Statistical Treatment
>
> Before and after the application of 4-AP, Student t tests were used to compare recovering action potential between the control and PEG-treated group. Comparisons of action potential amplitude were also made between the two PEG-treated groups. (page 20, lines 18-22 of the specification).

Further, Appellants also direct the Examiner and the Board to Example 2, entitled "Potassium Channel Blockade as an Adjunct to PEG-Mediated Recovery of Conduction" (page 24, line 17 to page 25, line 27 of the specification), Figure 6A-6C (depicting data from PEG/4-AP treated spinal cords), and the brief description of Figure 6 (page 6, lines 5-10 of the specification). Appellants submit that the Examiner has failed to recognize and consider the unexpected results achieved in the methods of claims 30, 40, and 43.

For at least the reasons set forth herein and previously of record, it is respectfully submitted that claims 22, 24-30, 38-40, and 43-44 are not unpatentable under 35 U.S.C. §103(a) over Balasubramanian in view of Potter et al. Review and reversal of this rejection of the claims under 35 U.S.C. § 103 by the Board is respectfully requested.

D. Claims 22-30, 38-40, 43, and 44 are patentable under 35 U.S.C. §103(a) over Shulman (U.S. Patent No. 4,599,354) in view of Edwards (U.S. Patent No. 4,369,769).

Claims 22-30, 38-40, 43, and 44 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Shulman (U.S. Patent No. 4,599,354) in view of Edwards (U.S. Patent No. 4,369,769) (pages 10-11, Office Action mailed February 23, 2005). Appellants' arguments set forth in the Appeal Brief mailed November 23, 2005, in response to this rejection are maintained and supplemented herewith.

Appellants respectfully submit that Shulman in view of Edwards does not teach contacting an injured spinal cord with *an effective amount* of at least one C1-C10 polyalkylene glycol or polyethylene glycol, wherein *the effective amount* of the at least one C1-C10 polyalkylene glycol or the polyethylene glycol *is effective to restore nerve impulse conduction through said injured spinal cord.* In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that Shulman "clearly teaches the effective amount of PEG being employed since the amount of PEG disclosed in Shulman is 2.3%. The resulting effect (i.e., restore nerve impulse conduction through the injured spinal cord) must be present . . . since the [p]roducts with identical chemical compositions and its properties are inseparable" (page 13, Examiner's Answer mailed February 27, 2006). Appellants disagree and submit that Shulman teaches PEG for use only as a suspending agent in a composition to be injected for pain relief (see column 2, lines 46-49).

In the "Response to Arguments" section of the Examiner's Answer, the Examiner asserted that "Appellants arguments . . . averring the synergistic effect of PEG and 4-aminopyridine are not convincing" (page 14 Examiner's Answer mailed February 27, 2006). Appellant's response to this assertion is as previously discussed in Section C, above. Further, as previously presented (page 19, Appeal Brief filed November 23, 2005), Appellants submit that neither Shulman nor Edwards provide any teachings or suggestions of 4-aminopyridine. Thus, Shulman in view of Edwards does not teach or suggest all of the limitations of the methods of claims 30, 40, and 43.

For at least the reasons set forth herein and previously of record, it is respectfully submitted that claims 22-30, 38-40, 43, and 44 are not unpatentable under 35 U.S.C. §103(a) over Shulman in view of Edwards. Review and reversal of this rejection of the claims under 35 U.S.C. § 103 by the Board is respectfully requested.

CONCLUSION

For the foregoing reasons, Appellants respectfully request that the Board review and reverse the rejections of claims 22-30, 38-40, 43, and 44 as discussed herein, and further that the Board direct the issuance of a Notice of Allowance of claims 22-30, 38-40, 43, and 44.

Respectfully submitted,

PURDUE RESEARCH
FOUNDATION
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
(612)305-1220

April 27, 2006
Date

By: Nancy A. Johnson
Nancy A. Johnson
Reg. No. 47,266
Direct Dial: (612) 305-4723